

Debarment Certification

NDA Application No.: 20-928

Drug Name: **Glucagon for Injection (rDNA origin)**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Jennifer L. Stotka, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 

Jennifer L. Stotka, M.D.

Title: Director, U.S. Regulatory Affairs

Date: December 10, 1997

Lilly

ORIGINAL

Lilly Research Laboratories

A Division of Eli Lilly and Company

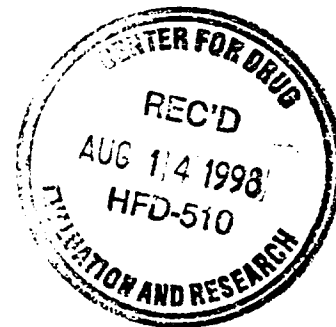
ORIG AMENDMENT

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Safety Update



Re: NDA 20-928; Glucagon for Injection (rDNA origin)

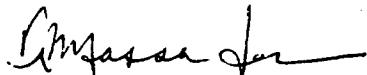
Reference is made to the submission (December 11, 1998) of a New Drug Application (NDA) for Glucagon for Injection (rDNA origin).

Per an August 12, 1998 phone conversation between Ms. Julie Rhee (Food and Drug Administration) and Dr. Kim Birch (Eli Lilly and Company) and per the requirements of 21 CFR §314.50(d)(5)(vi)(b) we are herewith submitting the requested safety update. No new safety information in animals or humans is available for rGlucagon. All patients enrolled in the rGlucagon clinical trials completed the study and follow-up at the time of NDA submission and no additional animal studies have been performed. For safety information on animal-source glucagon, please refer to the NDA annual report for animal glucagon that was submitted on February 2, 1998 to NDA 12-122.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Gregory Enas, Ph.D.

Director

US Regulatory Affairs

CC: Ms. Julie Rhee (FDA, HFD-510)
Dr. Robert Misbin (FDA, HFD-510)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
8-26-98	
CSO INITIALS	DATE

LAJ

/S/

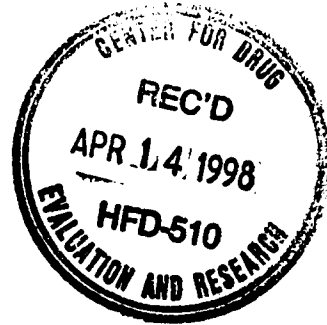
8/25/98

ORIGINAL

13M
Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



April 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room, 14B-14
5600 Fishers Lane
Rockville, MD 20857-1706

4-Month Safety Update

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to the submission (December 11, 1998) of a New Drug Application (NDA) for Glucagon for Injection (rDNA origin).

Per the requirements of 21 CFR §314.50(d)(5)(vi)(b) we are herewith submitting the requisite 4-month safety update. No new safety information in animals or humans is available for rGlucagon. All patients enrolled in the rGlucagon clinical trials completed the study and follow-up at the time of NDA submission and no additional animal studies have been performed. For safety information on animal-source glucagon, please refer to the NDA annual report for animal glucagon that was submitted on February 2, 1998 to NDA 12-122.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
US Regulatory Affairs

CC: Julie Rhee (FDA)
Robert Misbin (FDA)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS */S/* DATE 4-22-98

Noted
/S/
4/14/98

JAN 8 1997

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 7, 1998

From: Mathematical Statistician (HFD-715)

Through: Ed Nevius, Ph.D.
Director of Division of Biometrics 2
(HFD-715)

Subject: Statistical review not needed

To: File (NDA 20-928)

I have reviewed the documents submitted for NDA 20-928 (Glucagon). The studies presented to establish efficacy are PK/PD bioequivalence studies that do not require statistical input and therefore a review is not needed for this NDA.

/S/

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius/S/ 1-8-97

cc:
Orig. NDA 20-928
HFD-510
HFD-510/JRhee, RMisban, HAhn
HFD-715/DOB 2 File, Chron, ENevius, JMele

Mele/827-6376/DOB2/WordPerfect-glucagon.mem/Jan 7, 1998

This memorandum contains 1 page.

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon: 01/07/98
From: Robert M. Shore, Pharm.D.
Re: NDA 20-928/N-000
rGlucagon
Lilly
Participants: Robert M. Shore (FDA); Jim Woodworth (Lilly)

/S/

JAN - 7 1998

Jim Woodworth called yesterday, 01/06/98, to explain why there are discrepancies between the IND and NDA bioequivalence data (see teleconference memo 01/05/98). Jim called back today to add further explanation. He stated that, in the IND, only mean log-transformed data was used to generate 90% confidence interval estimates for the assessment of bioequivalence. In the NDA, a more complete ANOVA was used which included period and sequence effects and generated least squared means which were used for the 90% confidence interval estimates. This, he stated, explains why the IND results are different from the NDA results. Indeed, I told him that one of my comments on the IND review was about the lack of information on the statistical model, if any, that was used to calculate bioequivalence parameters.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

**APPEARS THIS WAY
ON ORIGINAL**

R/HEE

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon: 01/06/98
From: Robert M. Shore, Pharm.D. /S/
Re: NDA 20-928/N-000
rGlucagon
Lilly
Participants: Robert M. Shore (FDA); Jim Woodworth (Lilly)

JAN - 7 1998

Jim Woodworth called to explain why there are discrepancies between the IND and NDA bioequivalence data (response to Teleconference on 01/05/98). Jim stated that the IND preliminary report was just that - a 'preliminary report'. When it was generated, the actual blood collection times for every individual were not known; therefore, some nominal (scheduled) collection times were used to calculate pharmacokinetic parameters. With the NDA, actual collection times are used in all individuals.

In follow-up, I spot-checked some glucagon AUC calculations using the actual collection times; the results support this explanation.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

JAN - 5 1998

Date of Telecon: 01/05/98
From: Robert M. Shore, Pharm.D. /S/
Re: NDA 20-928/N-000
rGlucagon
Lilly
Participants: Robert M. Shore (FDA); Kim Birch (Lilly)

Kim Birch (317-277-1443) returned my call. I pointed out to her that there are discrepancies between the IND bioequivalence data (IND 51,559/N-012 cover letter 04/28/97) and the NDA data for the different rGlucagon formulations. The example I gave was summary tables for 90% confidence intervals (page 2109-2110 of the IND and V1.21, p 105 of the NDA). Although the ratios reported in the NDA are inverted from those reported in the IND, this does not account for the discrepancy. Indeed, even individual pharmacokinetic parameters appear to differ between the submissions.

Kim stated that she would contact Jim Woodworth and he may contact me directly.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 11, 1998

APPLICATION NUMBER: 20-928; Glucagon (rDNA) for Injection

BETWEEN:

Name: Mary Ann Holovac, HFD-
(301) 827-5470

AND

Name: Julie Rhee, HFD-510

SUBJECT: Exclusivity

I called Mary Ann to inquire about an exclusivity of this NDA. I mentioned that this NDA was submitted as 505(b)(1) and the sponsor had conducted bioequivalence studies plus a small safety study. I asked Mary Ann if a safety study qualifies for an exclusivity. Mary Ann told me usually a safety study does not qualify for an exclusivity and they (including generic) will decide whether or not this NDA qualifies for an exclusivity.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/

Julie Rhee

cc: Original 20-928
HFD-510/Div. File
HFD-510/Julie Rhee

APPEARS THIS WAY
ON ORIGINAL

TELECON

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: August 19, 1998
<p>Background: The animal-sourced glucagon (NDA 12-122) had a separate patients package insert for (1) diagnostic use, and (2) emergency use kit. However, this NDA contains a single patients package insert.</p> <p>_____</p> <p>I called Dr. Birch and mentioned that only one patients package insert was submitted in this NDA and asked if this insert is for diagnostic use, or for emergency use. Dr, Birch informed me that since patients package insert for diagnostic use, and emergency use are the same, they decided to go with a single patients package insert.</p> <p>cc:OrigNDA HFD-510/DivFile HFD-510/Misbin/HRhee/Berlin</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>_____/S/_____ Name: Julie Rhee</p>	<p>NDA#: 20-928</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA By: Telephone</p> <p>Product Name: Glucagon (rDNA origin) for Injection</p> <p>Firm Name: Eli Lilly</p> <p>Name and Title of Person with whom conversation was held: Kim Birch, Ph.D. Regulatory Affairs</p> <p>Phone: (317) 277-1443</p> <p>APPEARS THIS WAY ON ORIGINAL</p>

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: August 12, 1998
<p>I called Dr. Birch and requested the following:</p> <ol style="list-style-type: none">1. Since the last safety update was submitted in 4/98, another safety update submission is needed.2. On 6/6/98 submission: a clarification is needed for "sufficient" for item #6, under drug substance, and item #1, under drug product. They can clarify "sufficient" in terms of the number of batches or in terms of months or years. <p>Dr. Birch agreed to submit a safety update before the end of this week.</p> <p>cc:OrigNDA HFD-510/DivFile HFD-510/Misbin/Berlin</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>/S/</p> <p>Name: Julie Rhee</p>	<p>NDA#: 20-928</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA By: Telephone</p> <p>Product Name: Glucagon</p> <p>Firm Name: Eli Lilly</p> <p>Name and Title of Person with whom conversation was held: Kim Birch, Ph.D. Regulatory Affairs</p> <p>Phone: (317) 277-1443</p> <p>APPEARS THIS WAY ON ORIGINAL</p>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-928

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

JUN 11 1998

Dear Dr. Stotka:

We acknowledge receipt on June 9, 1998, of your June 8, 1998, amendment to your new drug application for Glucagon (rDNA origin) for Injection.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 12, 1998.

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**RECORD OF TELEPHONE
CONVERSATION/MEETING****Date:**
June 5, 1998

Submission date: 12/11/97, 1/16 and 4/5/98

When Dr. Birch returned my call, I informed her that on 5/4/98 labeling amendment, page 3, Figure 1, the number of normal volunteers should be changed from 29 to 25 because the number of subjects that completed the 1 mg SQ treatment with the rDNA glucagon pH=2.0 was 25.

She said she will verify the number and submit a revised labeling.

She also mentioned that a major CMC amendment will be submitted on Monday (June 8) by over night express. I asked her to include a desk copy. She agreed.

cc:OrigIND
HFD-510/DivFile
HFD-870/Shore
HFD-510/Berlin

NDA#: 20-928**Telecon/Meeting
initiated by:**

☐ Applicant/Sponsor
☒ FDA

By: Telephone**Product Name:**
Glucagon (rDNA)**Firm Name:**
Eli Lilly**Name and Title of Person
with whom conversation
was held:**
Kim Birch, Ph.D.
Regulatory Affairs**Phone:**
(317) 277-1443

/S/

Name: Julie Rhee

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
May 26, 1998

Re: Our 5/20/98 CMC fax to Lilly

Dr. Berlin and I called Dr. Birch to discuss Lilly's response to our 5/20/98 CMC fax. Dr. Birch assured us that we could expect their response to our fax no later than June 8.

I informed Dr. Birch that their response will constitute as a major amendment and will extend the review clock by 90-days. She said she understood.

Dr. Berlin informed her that he was informed by compliance the acceptable EER report could be expected by the end of this week.

I asked Dr. Birch to wait for biopharm labeling comments before they submit a labeling amendment. She agreed.

cc:OrigNDA 20-928
HFD-510/DivFile
HFD-510/Berlin

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/

Name: Julie Rhee

NDA#: 20-928

**Telecon/Meeting
initiated by:**

☐ Applicant/Sponsor

☒ FDA

By: Telephone

Product Name:
Glucagon (rDNA origin) for
Injection

Firm Name:
Eli Lilly

**Name and Title of Person
with whom conversation
was held:**

Kim Birch, Ph.D.
Regulatory Affairs

Phone:
(317) 277-1443

APPEARS THIS WAY
ON ORIGINAL

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
May 22, 1998

Re: May 4, 1998 submission

I called Dr. Birch and requested to substitute "... a slight ..." with "... an ..." under the *Carcinogenesis, Mutagenesis, Impairment of Fertility* section. Dr. Birch agreed to make the change in their labeling revision #4.

APPEARS THIS WAY
ON ORIGINAL

cc:OrigNDA
HFD-510/DivFile
HFD-510/Steigerwalt/HRhee

APPEARS THIS WAY
ON ORIGINAL

NDA#: 20-928

**Telecon/Meeting
initiated by:**

☐ Applicant/Sponsor

☒ FDA

By: Telephone

Product Name:
Glucagon (rDNA) for
Injection

Firm Name:
Eli Lilly

**Name and Title of Person
with whom conversation
was held:**


Kim Birch, Ph.D.
Regulatory affairs

Phone:
(317) 277-1443

APPEARS THIS WAY
ON ORIGINAL

Name: Julie Rhee

Rhee

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: May 21, 1998
<p>Re: Our fax dated 5/20/98</p> <p>I called Dr. Birch and informed her that there was a typo on our 5/20/98 fax on CMC review comments. I informed her that under the "Labeling"</p> <p>Dr. Birch mentioned that they had caught the mistake. However, since this product has more than one pharmacological class (i.e., anti-hypoglycemic and smooth muscle relaxer), she wanted Drs. Misbin, Berlin, and Moore discuss how to handle it. I told her I'll look into it.</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>cc:OrigNDA HFD-510/DivFile HFD-510/Berlin/Moore</p> <p>APPEARS THIS WAY ON ORIGINAL</p> <p>/s/</p> <p>Name: Julie Rhee</p>	<p>NDA#: 20-928</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: Glucagon (rDNA origin) for Injection</p> <p>Firm Name: Eli Lilly</p> <p>Name and Title of Person with whom conversation was held: Kim Birch, Ph.D. Regulatory Affairs</p> <p>Phone: (317) 277-1443</p> <p>APPEARS THIS WAY ON ORIGINAL</p> 

NDA 20-928

JAN 23 1998

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

Please refer to your December 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucagon (rDNA origin) for Injection.

We also refer to our acknowledgement letter dated December 18, 1997, which stated that the therapeutic drug review classification for this application would be decided at the filing meeting.

Our policy regarding determination of priority or standard review status is based on the proposed indications and alternate treatment(s) marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review.

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

✓ /S/ 1-23-98
Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-928

DEC 18 1997

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Glucagon for Injection (rDNA origin)

Therapeutic Classification: To be decided at filing meeting

Date of Application: December 11, 1997

Date of Receipt: December 12, 1997

Our Reference Number: 20-928

APPEARS THIS WAY
ON ORIGINAL

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 10, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/s/ 12/18/97
Enid Galters
Chief, Project Management Staff
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Lilly ORIGINAL *BC*

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



August 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides additional details for the responses to two chemistry, manufacturing, and control questions submitted June 8, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Tobias Massa

Tobias Massa, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

enclosure

*Noted
Acceptable
8/27/98*

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE
<i>/S/</i>	8-27-98



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine

Drug Products, HFD-510

Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Replacement of
Missing Pages

Re: NDA 20-928, Glucagon for Injection (rDNA origin)

We are herewith submitting 6 pages to NDA 20-928 that were inadvertently left out of the original submission. This information describes the methods for the glucagon radioimmunoassay used to measure glucagon levels in human plasma. This information was sent via facsimile from Dr. Kim Birch (Eli Lilly and Company) to Mr. Robert Shore (FDA) on June 16, 1998 as requested. A 1-page "place-holder" titled "Appendix A. Method ICD 32" can be found in NDA 20-928, volume 1-22, page 200. This information should follow this place-holder. We apologize for any inconvenience this may have caused.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory Enas, Ph.D.

Director

U.S. Regulatory Affairs

Enclosure

CC: Ms. Julie Rhee (FDA, HFD-510)



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



June 11, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine

Drug Products, HFD-510

Attn: Ms. Julie Rhee

5600 Fishers Lane

Rockville, MD 20857-1706

Correspondence

Draft Labeling Revision #4

(Diskettes provided)

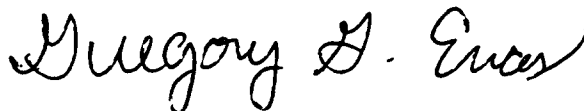
Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to phone conversations between Ms. Julie Rhee (FDA) and Dr. Kim Birch, Eli Lilly and Company (Lilly) on May 22, 1998 and June 4, 1998 and between Dr. John Holcombe (Lilly) and Dr. Robert Misbin (FDA) on May 20, 1998 regarding draft labeling for NDA 20-928, Glucagon for Injection (rDNA origin). We are herewith providing new draft labeling (revision #4) that addresses the suggested labeling revisions (Attachment 1). All labeling changes are depicted in a **large bold italicized font** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskette has been determined to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Gregory Enas, Ph.D.
Director
US Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Attachment

CC: Dr. Robert Misbin (FDA) Desk Copy (paper copy only)

APPEARS THIS WAY
ON ORIGINAL



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIG AMENDMENT

ORIGINAL



June 8, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides responses to the chemistry, manufacturing, and control questions received by fax on May 20, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Tobias Massa, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

enclosure

desk copy: Ms. Julie Rhee

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
/S/		8-3-98
CSO INITIALS		DATE

Action Pending



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CDER AMENDMENT

BL

Disc
V. 5.1.13



May 4, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510

Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #3

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a Facimile sent from Ms. Julie Rhee (FDA), to Dr. Kim Birch, Eli Lilly and Company (Lilly) on April 22, 1998 that summarized the Pharmacology Reviewer comments for NDA 20-928, Glucagon for Injection (rDNA origin) and suggested changes to the draft physician package insert (Attachment 1). We are herewith providing new draft labeling that addresses the proposed labeling revisions (Attachment 2). In addition we are providing minor changes to the carton labeling (Attachment 3). All labeling changes are depicted in a **different large bold font** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskettes have been determined to be free of viruses.

DUPLICATE

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



for: Jennifer L. Stotka, MD
Director
US Regulatory Affairs
Enclosures

APPEARS THIS WAY
ON ORIGINAL

CC: Ms. Julie Rhee (FDA) cover letter, diskettes
Dr. Herman Rhee (FDA) Desk Copy (cover letter, document, no disk)
Dr. Robert Misbin (FDA) Desk Copy (cover letter, document, no disk)

APPEARS THIS WAY
ON ORIGINAL

ORIG AMENDMENT

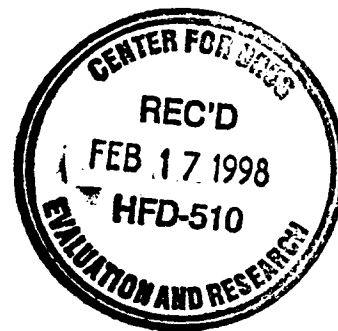
ORIGINAL

Lilly

Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



February 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides the responses to the microbiology questions received on February 4, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Tobias Massa

Tobias Massa, Ph.D.

Director

Regulatory Affairs (Chemistry, Manufacturing, and Control)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>TS/</i>	<i>4-14-98</i>
CSO INITIALS	DATE

Micro consult was sent & the review has been completed.

noted TS/ 4/13/98

enclosure

desk copy: Dr. William Berlin

Noted 3/11/98 TS/

Lilly

NEW CORRESP

ORIGINAL

Lilly Research Laboratories

A Division of Eli Lilly and Company

January 27, 1998

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine

Drug Products, HFD-510

Correspondence

Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706



Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a phone conversation between Dr. Herman Rhee, FDA Pharmacologist and Dr. Kim Birch, Eli Lilly and Company (Lilly) on January 13, 1998 in which Dr. Rhee requested information on the cardiovascular effects (e.g. heart rate, blood pressure, and inotropic effects) of recombinant glucagon observed in animal (dog) and human studies and a comparison of this information to known cardiovascular effects of Lilly's

We are herewith providing a summary of the nonclinical cardiovascular pharmacology studies with recombinant glucagon and a discussion of the cardiovascular effects observed with Lilly's animal-derived glucagon published in the literature (Attachment 1). In addition, we include a summary of the cardiovascular effects of glucagon in humans. Specifically, observations from Lilly clinical trials, one of which compares animal-derived glucagon directly to recombinant glucagon, are discussed (Attachment 2).

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
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<input type="checkbox"/> MEMO	
CSO INITIALS	DATE
<i>JS</i>	<i>4/13/98</i>

CC: Dr. Herman Rhee (FDA) Desk Copy
Dr. Robert Misbin (FDA) Desk Copy

rec'd
JS
4/13/98

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4/13/98

JS
4/13/98

Lilly

ORIGINAL

Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 26, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine

Drug Products, HFD-510

Attn: Dr. Solomon Sobel
5600 Fishers Lane
Rockville, MD 20857-1706



CORRESPONDENCE

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Eli Lilly and Company (Lilly) would like to thank you for recognizing the importance of Glucagon for Injection (rDNA origin) by assigning the NDA a Priority Review. The ability to offer patients a reliable supply of glucagon that is independent of the use of animal glands is a high priority for the company. Plans to shutdown and demolish our animal insulin/glucagon manufacturing facility has been expedited and aggressive target dates set for the opening of our new recombinant DNA manufacturing facility following news of the Priority rating. When we begin the transition from the old to the new facility and from animal-derived to recombinant DNA-derived manufacturing processes, Lilly intends to exhaust supplies of animal glucagon prior to launching our recombinant glucagon product. The goal of this strategy is to minimize the likelihood of a shortage of this critical care product in the market. Again, Lilly thanks you for acknowledging the significant benefits to patients that recombinant glucagon offers.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka
Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

/S/ *3-18-98*

CC: Dr. Alexander Fleming (FDA)
Dr. Robert Misbin (FDA)

noted
/S/
3/17/98

noted
/S/
1/29/98

noted
3/11/98
/S/

ORIG AMENDMENT

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



January 16, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides the responses to the biopharm questions received on January 13, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-4125 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory C. Davis

Gregory C. Davis, Ph.D.
Director

Regulatory Affairs (Chemistry, Manufacturing, and Control)

REVIEWS COMPLETED	
CSO ACTION:	
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<i>/S/</i>	4-6-98
CSO INITIALS	DATE

1/31
7/2/98

1/2/98

1/31

enclosure

desk copy: Dr. William Berlin

Noted
3/11/98
/S/

Lilly

ORIGINAL

Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 8, 1998



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine

Drug Products, HFD-510
Attn: Ms. Julie Rhee (desk copy)
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Per your request we are providing you with an electronic copy of the Information for the Physician and Information for the Patient draft package inserts for Glucagon for Injection (rDNA origin) that were included in NDA 20-928. Both inserts are in Microsoft Word format and are provided on a diskette that has been verified to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	8-24-98
CSO INITIALS	DATE

enclosure



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 6, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

**CORRESPONDENCE
CORRECTION**

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Please disregard the correspondence dated December 12, 1997 that was submitted to NDA 20-928 in error. We apologize for any inconvenience this may have caused you.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
US Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

cc: Ms. Julie Rhee (FDA)

**Lilly Research Laboratories**

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 12, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706**CORRESPONDENCE****Re: NDA 20-928; Glucagon for Injection (rDNA origin) - Electronic Media**

The enclosed materials were omitted inadvertently from yesterday's submission. We apologize for any inconvenience. This packet contains information specifically requested to be delivered to Dr. Robert Shore. It provides a compilation of background information and rationale for a priority rating, as well as previous correspondence and slides from the pre-NDA meeting in March of 1997, and information on Lilly study H3F-LC-GFAA.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Reviewing
Desk
copy
/S/
12/19/97

enclosures

cc: Dr. Robert Shore (FDA, HFD-870)



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



December 11, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510

CORRESPONDENCE

Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-928; Glucagon for Injection (rDNA origin) - Electronic Media

Eli Lilly and Company (Lilly) is herewith submitting a single CD-ROM disk that contains an identical electronic copy of items 1, 2, 3, 6, 8, 10, 11 and 12 from the Glucagon for Injection (rDNA origin) NDA. All files on the CD-ROM disk are in Adobe PDF format. Please note that the case report tabulations and case report forms, usually included in items 11 and 12 respectively, are included as part of the clinical study reports located in items 6 and 8. Two diskettes containing Part 1 and Part 2, respectively of the pharmacokinetic and pharmacodynamic datasets and output files from study GFAA (NDA Item 6) are included in three formats ("txt" = tab-delimited ASCII files, ".prn" = space-delimited ASCII files, and ".xls" = Excel files) for use by the Biopharmaceutics group as requested. We are also including three additional copies of NDA Volume 1.1 as requested.

If you have any questions concerning the functionality of the CD-ROM, please contact:

Steven T. Ward
(317) 276-2952 (work)
(317) 256-8888 (pager)

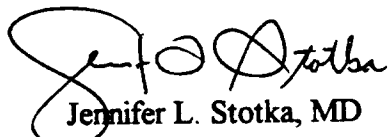
If you have any questions concerning the functionality of the electronic media containing the pharmacokinetic and pharmacodynamic datasets, please contact:

Dr. Jim Woodworth
(317) 276-1304 (work)

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

enclosures

CC: Cover letter to:
Dr. Robert Shore (FDA, HFD-870)

APPEARS THIS WAY
ON ORIGINAL



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 11, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NEW DRUG APPLICATION

Re: NDA 20-928—Glucagon for Injection (rDNA origin)

This letter accompanies the submission by Eli Lilly and Company (Lilly) of an original New Drug Application (NDA) for Glucagon for Injection (rDNA origin) [referred to as rGlucagon] to support the indications for the treatment of hypoglycemia and for use as a diagnostic aid for radiologic examinations. Currently, animal-derived Glucagon for Injection is approved for these indications.

This 38 volume NDA contains clinical data from two clinical studies; a pharmacokinetic/pharmacodynamic study in healthy volunteers that used animal-derived glucagon as the comparator (GFAA) and a safety study in healthy volunteers that measured rGlucagon stimulated antibody formation (immunogenicity) compared with animal-derived glucagon (GFAB).

Lilly believes that the NDA for Glucagon for Injection (rDNA origin) warrants an expedited review. The rationale for this conclusion is described in the Regulatory Background Information section located in the first volume.

Lilly has discussed the registration plans for rGlucagon with the FDA personnel. These meetings and communications have been summarized in the Regulatory Background Information section of this application included in volume 1. The understandings and agreements reached between Lilly and the FDA have been incorporated into this application.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications". An identical electronic copy of items 1, 2, 3, 6, 8, 10, 11 and 12 has been provided on a single CD-ROM disk. All files on the CD-ROM disk are in Adobe PDF format. A diskette containing the pharmacokinetic and pharmacodynamic datasets and output files will be provided to the Biopharmaceutics group as requested.

All electronic media have been checked by Lilly Information Technology personnel and have been verified to be free of known viruses.

As required by regulations, we hereby certify that the field copy is being provided simultaneously to our home FDA district office in Detroit, Michigan and that this copy contains all appropriate sections, identical to those provided to the reviewing division. Lilly affirms that all manufacturing sites listed in this application that are involved in the manufacturing, packaging and labeling of Glucagon for Injection (rDNA origin) are available for pre-approval inspection.

The initial User Fee for this submission has been paid under User Fee . This fee amount was determined using the fee structure for fiscal year 1997 under PDUFA 1 as recommended by Mr. Tom Hassel (FDA) in a phone conversation with Dr. Kim Birch (Lilly) on November 17, 1997 with the understanding that the remainder of the User Fee will be billed according to PDUFA 2 fee structure at a later time. Form 3397 is provided.

A Debarment Certification has been provided.

To facilitate the review of this application, we suggest that any facsimile (FAX) or other written communication, regardless of subject, be directed to:

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15 p.m. (EST). Any calls concerning general issues, clinical reports and labeling should be made to:

Kim Birch, Ph.D.
(317) 277-1443 (work)
(317) 256-6033 (pager)
(317) 834-2743 (home)

or alternatively you may reach Dr. Birch via E-mail at Kbirch@Lilly.com

In case of Dr. Birch's absence please contact:

Jennifer L. Stotka, M.D.
(317) 276-1249 (work)
(317) 257-7606 (home)

Any telephone calls related to manufacturing and control issues should be made to:

Gregory Davis, Ph.D.
(317) 276-4125 (work)
(317) 581-9101 (home)

or in his absence to:

Ann Maloney
(317) 276-0156 (work)
(317) 259-1198 (home)

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Philip R. Reid, M.D.
Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Enclosures

cc: Desk copies: Cover Letter and Regulatory Background Information only to:

Dr. Hae-Young Ahn (HFD-870)
Dr. James Bilstad (HFD-102)
Dr. G. Alexander Fleming (HFD-510)
Ms. Enid Galliers (HFD-511)
Dr. Robert Misbin (HFD-510)
Dr. Stephen Moore (HFD-510)
Ms. Julie Rhee (HFD-510)
Dr. Robert Shore (HFD-870)
Dr. Solomon Sobel (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF INDEX

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ITEM 5 Nonclinical Pharmacology and Toxicology Section	1.15 - 1.20
ITEM 6 Human Pharmacokinetics and Bioavailability Section	1.21 - 1.23
ITEM 7 Microbiology Section	1.24
ITEM 8 Clinical Section	1.25 - 1.30
ITEM 9 Safety Update Report	Not Applicable
ITEM 10 Statistical Section	1.31 - 1.36
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